REMARKS

Status of the Claims.

Claims 26-28, 56, and 61-63 are pending with entry of this amendment, no claims being cancelled and no claims being added herein. Claims 26 and 28 are amended herein for clarity. These amendments introduce no new matter. Support is replete throughout the specification.

35 U.S.C. §112, Second Paragraph.

Claims 26-28, 37, 56, and 61-63 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because, according to the Examiner, the term "relative copy number" is indefinite. Applicants have previously explained that the term "relative copy number" is a term of art well known and understood in the field. It will be appreciated that the relative copy number can be determined relative to any convenient control.

Nevertheless, for the purposes of clarity claim 26 is amended herein to simply recite ". . . detecting the formation of a hybridization complex to determine **a** copy number of a nucleic acid in chromosomal region 20q13.2; . . . " thereby obviating this rejection. It will be appreciated by one of skill in the art that a copy number can be a relative copy number or an absolute copy number and either is adequate for the purposes of the recited/claimed assay.

35 U.S.C. §112, First Paragraph - Written Description.

The Examiner rejected claims 26-28, 56, 61-63 under 35 U.S.C. §112, first paragraph, as allegedly not enabled because "the claims as written encompass a method for detecting the presence or absence of neoplastic cells . . . . using probes with unknown structure and length provided said probes share a fragment with SEQ ID NO:9 and are capable of hybridizing to SEQ ID NO:9 via said common fragment under the stringent conditions recited in claims 26." The Examienr further asserted that the specification and claims lack information of the structure and function of the probes used for the claimed method and thus allegedly does not meet the written description requirement.

Applicants traverse. The Examiner is reminded that "[t]he written description requirement **does not require the applicant 'to describe exactly the subject matter claimed**, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. [emphasis added] '" *Union Oil Co. v Atlantic Richfield et al.* 208 F.3d

989 (Fed. Cir. 2000) *citing In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2D (BNA) 1614, 1618 (Fed. Cir. 1989).

In the present case, claims are directed to a method that utilizes probes that hybridize to a target polynucleotide sequence (SEQ ID NO:9) under particular recited stringent conditions. The generation of probes specific to target sequences is routine to those of skill in the art. Indeed such probes can be generated *ad nauseum* using commercially available software tools know to those of skill in the art (*e.g.* Oligodb available through PubMed, Sarani from Strand Genomics, Visual OMP from DNA software Ind., *etc.*). Thus, once a target nucleotide sequence is known probes that specifically hybridize to that sequence under stringent conditions are also *de facto* known to those of skill in the art.

In view of this there is simply no question that the specification, as filed, communicates to one of ordinary skill in the art that Applicants invented what is claimed. As stated by the Federal Circuit in *Union Oil:*

> If lack of literal support alone were enough to support a rejection under §112, then the statement of In re Lukach. . . that "the invention claimed does not have to be described in ipsis verbis in order to satisfy the description requirement of §112, is empty verbiage.

Thus, literal language describing every claimed species is not required to meet the description requirement. To the contrary, as evidenced in *Union Oil*, guidelines and functional descriptions leading one of skill to the claimed invention are sufficient to meet the description requirements.

In the present case, the specification provides the target sequence (SEQ ID NO:9) and a desired stringency. Suitable probe sequences are readily provided by routine use of probe design software packages or even by visual inspection of the sequence (for example the complement of SEQ ID NO:9) would readily be recognized as a suitable probe. Consequently, given the level of skill in the art, it is readily apparent that Applicants were in possession of the claimed invention.

Accordingly the claims meet the Written Description requirement and the rejection of claims 26-28, 56, 61-63 on these grounds should be withdrawn.

35 U.S.C. §112, First Paragraph - Enablement.

Claims 26-28, 37, 56, and 61-63 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled because:

1) Applicants have allegedly failed to establish that ZABC-1 is amplified in the 20q13.2 amplicon; and

2) Allegedly no specific probes are recited for use in the detection of SEQ ID NO:9.

1) Amplification of ZABC-1.

Claims 26-28, 37, 56, and 61-63 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled. In particular, the Examiner alleged that Applicants have failed to establish that the recited sequencer (SEQ ID NO:9) is overexpressed in neoplastic cells having an amplification at 20q13.2. Applicants traverse.

The examiner is reminded that she **must treat as true** a statement of fact made by an applicant in relation to an asserted utility, unless **countervailing evidence** can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. [emphasis added] (Official Gazette, 66(4): 1099)

As stated by the Federal Circuit court of Appeals:

> . . . a specification disclosure which contains a teaching of the manner and process of using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patened *must* be taken as in compliance with the enabling requirement of the first paragraph of §112 *unless* there is reason to doub the objective truth of the statements contained therein. . . *Ex parte Sudilovsky* 21 USPQ2d 1703 (Fed. Cir., 1992) *citing In re Marzocchi*, 169 USQP 367 (CCPA 1971).

In the present case, it is established that a large (1.5 Mb) amplification at 20q13.2 is associated with cancers. It is also established that the recited sequence (SEQ ID NO:9) represents a region within this amplification.

Moreover, it is also generally known that chromosomal amplifications such as the one at 20q13.2 occur through gross chromosomal rearrangements such as translocations, inversions, failed segregation, and the like. Such gross rearrangemtns typically effect all of the nucleic acid sequences

within the amplified region. Thus, one of skill in the art would reasonably expect the recited sequence to be amplified in cells having the amplification at 20q13.2.

In addition, it is noted that SEQ ID NO:9 represents the ZABC-1 gene which is also known as ZNF217 (see attached printout of www.infobiogen.fr/ services/chromcancer/ genes_gc/GC_ZNF217.html attached as Exhibit A). **ZNF217 (ZabC1) has been shown to be amplified in colorectal cancers having a 20q13.2 amplification** (*see* Hidaka *et al.* (2000) *Clin. Cancer Res.*, 6: 2712-2717, attached as Exhibit B).

The Examiner has failed to provide any objective evidence to establish that the recited sequence is not amplified in the 20q13.2 amplification. To the contrary, the Examiner simply states:

> [I]t is well known in the art that amplification nor regulation of different genes is independent of each other. (Office Action, page 5, lines 21-22). This statement simply does not apply to the situation at hand.

Contrary to the Examiner's assertion, **it is well established that copy number of various genes located within a single contiguous amplification (such as is found at 20q13.2) is not independent**. Hence the contiguous nature of the amplification.

The Examiner's assertion amounts to little more than speculation lacking objective evidence. Absent any objective evidence and, in the face of published evidence showing that ZabC1 is amplified, Applicants understand the Examiner's position to be based on personal knowledge and belief. **Accordingly, should the Examiner wish to maintain this position, Applicants request the Examiner to provide an affidavit to this effect as required by 37 C.F.R. 1.107 (see M.P.E.P. 2144.03).**

In view of the foregoing, the Examiner has simply failed to meet her burden and establish by objective evidence that the recited sequence, which is known to be located within a gross chromosomal abnormality (the 20q13.2 amplification) is not amplified. Accordingly the rejection of claims 26-28, 37, 56, and 61-63 on these grounds should be withdrawn.

2) ZABC-1 Specific Probes.

The rejected claims 26-28, 56, 61-63 as not enabled alleging that no probes are identified. The Examiner further alleged that using any probe, non-related nucleic acids could be detected. Applicants traverse.

The claims **do not** read on the use of any probes. To the contrary, the claims, as amended, recite the use of probes that **specifically hybridize** to the target sequence under stringent conditions. The specification at page 6, lines 13-20 states:

> Bind(s) substantially" or "binds specifically" or "binds selectively" or "hybridizes specifically" refer to complementary hybridization between an oligonucleotide and a target sequence and embraces minor mismatches that can be accommodated by reducing the stringency of the hybridization media to achieve the desired detection of the target polynucleotide sequence. These terms also refer to **the binding, duplexing, or hybridizing of a molecule only to a particular nucleotide sequence under stringent conditions when that sequence is present in a complex mixture (e.g., total cellular) DNA or RNA**. [emphasis added]

The probes contemplated for use in the claimed method thus specifically bind (*e.g.* specifically detect) the recited target sequence and not other non-related sequences that may be present.

Moreover, the Examiner is reminded that "a patent need not teach **and preferably omits**, what is well-known in the art." [emphasis added] *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986) *cert. denied* 480 U.S. 947 (1987). As explained above, given a known target sequence (*e.g.* SEQ ID NO:9) the design of suitable specific probes is routine and well known to those of skill in the art.

The claimed method is thus fully enabled and the rejection of claims 26-28, 56, 61-63 on these grounds should be withdrawn.

35 U.S.C. §112, First Paragraph -- Scope.

Claims 26-28, 56, and 61-63 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled because:

1) The specification is allegedly not enabling for detecting the presence or absence of "any neoplastic cell" and;

2) The specification is alleged not enabling for a method of detecting in "any sample" the presence or absence of neoplastic cells having an increased copy number. Applicants traverse.

1) "Any neoplastic cell".

The Examiner's rejection of the claims as not enabled because the specification is allegedly not enabling for detecting the presence or absence of "any neoplastic cell" is based on a gross misreading of the plain language of the claims. Claim 26 expressly recites:

> 26. A method of detecting in a sample the presence or absence of **neoplastic cells having an increased copy number of nucleic acid sequences at chromosome region 20q13.2**, the method comprising: . . . [emphasis added]

The claim simply is not directed to detecting any neoplastic cell. To the contrary, as the highlighted language reveals, the claim is directed to a method of detecting a neoplastic cell having an increased copy number of nucleic acid sequences at chromosome region 20q13.2. The Examiner has offered no basis or rationale for ignoring express language on the face of the claim to in her assertion that the claim reads on a method of detecting any neoplastic cell. In making her rejection, the Examiner simply reads the claim more broadly than the plain language permits and this is an improper basis for a "scope rejection".

Moreover, as explained above, ZabC1 (SEQ ID NO:9) is located within the 20q13.2 amplicon and as asserted in the specification and supported by published data (*e.g.*, Exhibit B), ZabC1 is a gene that is amplified in the 20q13.2 amplicon.

The scope of the claims is comparable to the scope of the disclosure in the specification. Accordingly, Applicants have met the requirements of 35 U.S.C. §112, first paragraph, and the rejection of claims 28, 56, and 61-63 should be withdrawn.

2) "In any sample".

Claims 26-28, 37, 56, and 61-63 were rejected under 35 U.S.C. §112, first paragraph, as allegedly overbroad because the specification is allegedly not enabling for a method "for detecting in 'any sample' the presence or absence of neoplastic cells having an increased number of nucleic acid

sequences at chromosome region 20q13.2. In particular, the Examiner alleges that ". . . it is unpredictable that nay cancer cell or any cancer tissue would have an increased copy number of SEQ ID NO:9. . . ". As explained above, the Examiner persists in misreading the plain language of the claims. Claim 26 expressly recites:

> A method of detecting in a sample
> the presence or **absence** of
> **neoplastic cells having an increased copy number of nucleic acid sequences at chromosome region 20q13.2**: . . . [emphasis and formattign added]

In view of the highlighted language, the claim is plainly directed to detecting the presence **or absence** of neoplastic cells and the neoplastic cells are neoplastic cells having increased copy number of nucleic acid sequences at chromosome region 20q13.2.

The Examiner posits that the claimed method is not enabled for cells or tissues in a cancer where SEQ ID NO:9 is not amplified. This simply is not correct. In a cancer lacking a 20q13.2 amplification, the claimed method will provide a negative result. **In other words, in a cancer lacking a 20q13.2 amplification the method will detect the absence of neoplastic cells having an increased copy number of nucleic acids at 20q13.2.** The method thus works as claimed in any cell or tissue and is fully enabled for such.

The Examiner's comment regarding the alleged lack of use for the claimed detection of the absence of neoplastic cells in a sample (see Office Action, page 9, lines 13-14) simply does not negative enablement or indicate that the scope of the claims is overbroad.

The Examiner's allegation regarding the limited use of the claimed invention in certain contexts samples goes to utility rather than enablement. There is, however, no doubt that a method of detecting neoplastic cells has a specific, substantial and credible utility.

Again, Applicants have met the requirements of 35 U.S.C. §112, first paragraph, and the rejection of claims 28, 56, and 61-63 should be withdrawn.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. ***Should the Examiner seek to maintain the rejections, Applicants hereby expressly request, on the record, that the Examiner call Applicants to arrange a telephone interview with the Examiner and the Examiner's supervisor.***

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3513.

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Respectfully submitted,

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